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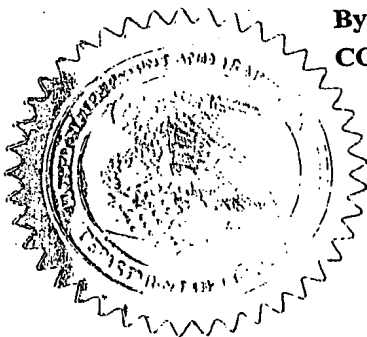
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Transmitted herewith for filing under 37 CFR §1.53(c) is the PROVISIONAL APPLICATION for patent of

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TITLE OF THE INVENTION (280 characters max)  ORGANIC COMPOUNDS		

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### ENCLOSED APPLICATION PARTS (check all that apply)

- ☒ Specification (Including Any Claims) - 9 pages  
☐ Drawings - sheets  
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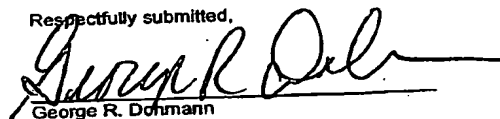
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Respectfully submitted,



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## ORGANIC COMPOUNDS

The present invention relates to salts forms of the pharmaceutically active compound 4-[(4-methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide.

The pharmaceutically active compound 4-[(4-methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide is commonly known by its INN name imatinib. Imatinib and its preparation are described in U.S. Patent No. 5,521,184.

Basic pharmaceutically active compounds are commonly formulated into pharmaceutical preparations as an acid addition salt form, particularly as a crystalline acid addition salt. For example, imatinib is marketed in many countries as its monomethanesulfonate salt (imatinib mesylate) under the brandname GLIVEC or GLEEVEC. Two crystal forms of imatinib mesylate are described in WO 99/03854. The crystal form designated as the beta form is described as having physical properties that make it advantageous for the manufacture of solid oral pharmaceutical dosage forms, such as tablet and capsule dosage forms.

Although it is known that the preparation of salt forms may improve the physical or pharmaceutical properties of a basic pharmaceutically active compound, it is not possible to predict which salt forms may possess advantages for a particular purpose prior to the actual preparation and characterization of the salt form. The present invention relates to salt forms of imatinib, other than imatinib mesylate, that are useful for the manufacture of solid or liquid pharmaceutical dosage forms, particularly solid oral dosage forms, such as tablets and capsules, and liquid oral dosage forms, such as orally administered solutions and suspensions, as well as suppositories and other pharmaceutical dosage forms. Each of these salt forms possesses one or more properties that provides advantages when used as a pharmaceutical active ingredient, such as physical properties that make it easier to manufacture one or more dosage forms, improved stability, improved bioavailability and other such properties that are known to one of skill in the art.

The salt forms of imatinib are prepared by methods known in the art for making acid addition salts of amines, e.g., by treatment of imatinib with an acid or a suitable anion exchange reagent. Typically, imatinib or a solution of imatinib is combined with a solution of

an organic or mineral acid in, e.g., a lower alcohol, such as methanol or ethanol, with or without heating. The salt is isolated by crystallization or by evaporation of the solvent and, if desired, purified by re-crystallization from an appropriate re-crystallization solvent by methods known to one of skill in the art.

Important embodiments of this invention include salts of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide selected from the group consisting of a tartrate salt, such as a (D)(-) tartrate salt or a (L)(+) tartrate salt, a hydrochloride salt, a citrate salt, a malate salt, particularly a D-malate salt, a fumarate salt, a succinate salt, a benzoate salt, a benzenesulfonate salt, a pamoate salt, a formate salt, a malonate salt, a 1,5-naphthalenedisulfonate salt, a salicylate salt, a cyclohexanesulfamate salt, a lactate salt, particularly a (S)-lactate salt, a mandelate salt, particularly an (R)(-) mandelate salt, a glutarate salt, an adipate salt, a squarate salt, a vanillate salt, an oxaloacetate salt, an ascorbate salt, particularly an (L)-ascorbate salt and a sulfate salt.

Further important embodiments of this invention include imatinib ascorbate, imatinib formate, imatinib malonate, imatinib oxaloacetate, imatinib squarate and imatinib vanillate.

The present invention further relates to a pharmaceutical composition comprising one of the above mentioned salts of imatinib and a pharmaceutically acceptable carrier.

In one embodiment, the invention relates to a pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an acid addition salt of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide selected from the group consisting of a tartrate salt, such as a (D)(-) tartrate salt or a (L)(+) tartrate salt, a hydrochloride salt, a citrate salt, a malate salt, particularly a D-malate salt, a fumarate salt, a succinate salt, a benzoate salt, a benzenesulfonate salt, a pamoate salt, a formate salt, a malonate salt, a 1,5-naphthalenedisulfonate salt, a salicylate salt, a cyclohexanesulfamate salt, a lactate salt, particularly a (S)-lactate salt, a mandelate salt, particularly an (R)(-) mandelate salt, a glutarate salt, an adipate salt, a squarate salt, a vanillate salt, an oxaloacetate salt, an ascorbate salt, particularly an (L)-ascorbate salt and a sulfate salt.

In an important embodiment, the acid addition salt is selected from the group consisting of imatinib ascorbate, imatinib formate, imatinib malonate, imatinib oxaloacetate, imatinib squarate and imatinib vanillate.

#### **Example 1**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, tartrate**

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) is added to a solution of (2*R*,3*R*)-2,3-dihydroxybutanedioic acid (*L*-(+)-tartaric acid; Fluka, Buchs, Switzerland; 1.50 g, 10 mmol) in hot ethanol (40 mL). The solution is evaporated to dryness under reduced pressure and the resulting residue is re-crystallized from methanol to afford, after filtering and drying, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, tartrate as a pale-yellow crystalline solid, having the following analytical properties: Analysis found: C, 60.18; H, 5.96; N, 14.86%; H<sub>2</sub>O, 2.25%. Calculated for C<sub>33</sub>H<sub>37</sub>N<sub>7</sub>O<sub>7</sub> · 0.82 H<sub>2</sub>O: C, 60.19; H, 5.91; N, 14.89%. H<sub>2</sub>O, 2.24%.

#### **Example 2**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, hydrochloride**

Aqueous hydrochloric acid (0.99 g of 37%) is added to a solution of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) in ethanol (20 mL). The solution is evaporated to dryness under reduced pressure and the resulting residue is re-crystallized from ethanol – ethylacetate. The product is filtered-off and re-crystallized from isopropanol to afford, after filtering and drying, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, hydrochloride as a pale-yellow crystalline solid, having the following analytical properties: Analysis found: C, 65.27; H, 6.07; N, 18.19; Cl, 6.55%; H<sub>2</sub>O, 0.56%. Calculated for C<sub>29</sub>H<sub>32</sub>N<sub>7</sub>OCl · 0.17 H<sub>2</sub>O: C, 65.33; H, 6.11; N, 18.39; Cl, 6.65%; H<sub>2</sub>O, 0.57%.

#### **Example 3**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, citrate**

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) is added to a solution of anhydrous 2-hydroxy-1,2,3-propanetricarboxylic acid (citric acid; Merck, Darmstadt, BRD; 1.92 g, 10 mmol) in methanol (30 mL) at room temperature. Upon cooling, 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, citrate crystallizes and is filtered and dried to afford a pale-yellow crystalline solid, having the following analytical properties: Analysis found: C, 59.24; H, 5.71; N, 13.60%, H<sub>2</sub>O, 2.14%. Calculated for C<sub>35</sub>H<sub>39</sub>N<sub>7</sub>O<sub>8</sub> · 0.83 H<sub>2</sub>O: C, 60.00; H, 5.85; N, 13.99%; H<sub>2</sub>O, 2.13%.

#### **Example 4**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, malate**

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) is added to a solution of (2S)-(-)-hydroxybutanedioic acid (L-(-)-malic acid; Fluka, Buchs, Switzerland; 1.34 g, 10 mmol) in water (40 mL). The mixture is heated and the resulting hot solution is filtered and evaporated to dryness under reduced pressure to give a residue which is re-crystallized from ethanol, filtered and dried to give 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, malate as a pale-yellow crystalline solid, having the following analytical properties: Analysis found: C, 62.88; H, 6.04; N, 15.60%; H<sub>2</sub>O, 0.45%. Calculated for C<sub>33</sub>H<sub>37</sub>N<sub>7</sub>O<sub>8</sub> · 0.16 H<sub>2</sub>O: C, 62.86; H, 5.97; N, 15.55%; H<sub>2</sub>O, 0.46%.

#### **Example 5**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, fumarate**

(*Trans*)-butenedioic acid (fumaric acid; Fluka, Buchs, Switzerland; 1.16 g, 10 mmol) is added to a solution of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) in ethanol (25 mL). The mixture is heated to 90°C, treated with water (18 g) and filtered. Upon cooling, the product crystallizes and is filtered and dried to afford 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, fumarate a pale-yellow crystalline solid, having the following analytical properties: Analysis found: C, 63.91; H, 5.99; N, 15.74%;

H<sub>2</sub>O, 1.27%. Calculated for C<sub>33</sub>H<sub>35</sub>N<sub>7</sub>O<sub>5</sub> · 0.44 H<sub>2</sub>O: C, 64.18; H, 5.86; N, 15.88%; H<sub>2</sub>O, 1.28%.

#### **Example 6**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, succinate**

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) is added to a solution of butanedioic acid (succinic acid; Fluka, Buchs, Switzerland; 1.18 g, 10 mmol) is added to a solution of in ethanol (25 mL). The mixture is heated to 90°C, treated with water (0.2 g) and filtered. Upon cooling, the product crystallizes and is filtered and dried to afford 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, succinate as a pale-yellow crystalline solid, having the following analytical properties: Analysis found: C, 64.19; H, 6.11; N, 15.82%; H<sub>2</sub>O, 0.87%. Calculated for C<sub>33</sub>H<sub>37</sub>N<sub>7</sub>O<sub>5</sub> · 0.30 H<sub>2</sub>O: C, 64.23; H, 6.14; N, 15.89%; H<sub>2</sub>O, 0.88%.

#### **Example 7**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, benzoate**

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) is added to a solution of benzoic acid (Fluka, Buchs, Switzerland; 1.22 g, 10 mmol) in xylene (50 mL). The mixture is heated and the resulting hot solution is filtered. Upon cooling, the product crystallizes and is filtered and dried to afford 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, benzoate as a pale-brown crystalline solid, having the following analytical properties: Analysis found: C, 70.13; H, 6.12; N, 16.24%. Calculated for C<sub>36</sub>H<sub>37</sub>N<sub>7</sub>O<sub>3</sub>: C, 70.22; H, 6.06; N, 15.92%.

#### **Example 9**

**4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, benzenesulphonate**

4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) is added to a solution of benzenesulphonic acid (Fluka, Buchs, Switzerland; 1.61 g, 10 mmol) in hot toluene (40 mL).



The solution is evaporated to dryness under reduced pressure and the resulting residue is re-crystallized from ethanol – ethylacetate. The product is filtered-off and dried to afford 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, benzenesulphonate as a pale-yellow crystalline solid, having the following analytical properties: Analysis found: C, 64.19; H, 5.68; N, 14.93; S, 4.87%; H<sub>2</sub>O, 0.34%. Calculated for C<sub>35</sub>H<sub>37</sub>N<sub>7</sub>O<sub>4</sub>S - 0.12 H<sub>2</sub>O: C, 64.28; H, 5.74; N, 14.99; S, 4.90%; H<sub>2</sub>O, 0.33%.

#### **Example 10**

##### **4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, pamoate**

A mixture of 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide (4.94 g, 10 mmol) and 4,4'-methylenebis[3-hydroxy-2-naphthoic acid (Fluka, Buchs, Switzerland; 3.88 g, 10 mmol) in ethanol (50 mL) is heated. Water (25 mL) is then added. Upon cooling, the product crystallizes and is filtered-off and dried to afford 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, pamoate as a pale-yellow solid, having the following analytical properties: Analysis found: C, 69.12; H, 5.62; N, 10.88%; H<sub>2</sub>O, 2.50%. Calculated for C<sub>62</sub>H<sub>47</sub>N<sub>7</sub>O<sub>7</sub> - 1.26 H<sub>2</sub>O: C, 69.04; H, 5.52; N, 10.84%; H<sub>2</sub>O, 2.51%.

Each of the following is prepared in accordance with methods known in the art, such as by a procedure analogous to that described in the cited reference:

- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, formate (from formic acid; Chem. Abstr. 64-18-6)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, malonate (from 1,3-propanedioic acid; Chem. Abstr. 141-82-2)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, 1,5-naphthalenedisulphonate (from 1,5-naphthalenedisulphonic acid; Chem. Abstr. 300394-97-2)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, salicylate (from 2-hydroxybenzoic acid; Chem. Abstr. 69-72-7)

- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, (*D*)-malate (from (2*R*)-(-)-hydroxybutanedioic acid; Chem. Abstr. 636-61-3)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, cyclohexanesulphamate (from *N*-cyclohexylsulphamic acid; Chem. Abstr. 100-88-9)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, (*S*)-lactate (from (2*S*)-(-)-2-hydroxypropanoic acid; Chem. Abstr. 79-33-4)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, (*R*)-(-)-mandelate (from (*R*)-(-)-alpha-hydroxybenzeneacetic acid; Chem. Abstr. 611-71-2)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, (*D*)-(-)-tartrate (from (2*S*,3*S*)-2,3-dihydroxybutanedioic acid; Chem. Abstr. 147-71-7)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, glutarate (from 1,5-pentanedioic acid; Chem. Abstr. 110-94-1)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, adipate (from 1,6-hexanedioic acid; Chem. Abstr. 124-04-9)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, squarate (3,4-dihydroxy-3-cyclobutene-1,2-dione; Chem. Abstr. 2892-51-5)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, vanillate (from 4-hydroxy-3-methoxybenzoic acid; Chem. Abstr. 121-34-6)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, oxaloacetate (from oxobutanedioic acid; Chem. Abstr. 328-42-7)
- 4-[(4-Methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, (*L*)-ascorbate (from vitamin C; Chem. Abstr. 50-81-7)

- 4-[(4-Methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide, sulphate (from sulphuric acid)

## Claims

1. An acid addition salt of 4-[(4-methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide selected from the group consisting of a tartrate salt, such as a (*D*)(-) tartrate salt or a (*L*)(+) tartrate salt, a hydrochloride salt, a citrate salt, a malate salt, particularly a *D*-malate salt, a fumarate salt, a succinate salt, a benzoate salt, a benzenesulfonate salt, a pamoate salt, a formate salt, a malonate salt, a 1,5-naphthalenedisulfonate salt, a salicylate salt, a cyclohexanesulfamate salt, a lactate salt, particularly a (*S*)-lactate salt, a mandelate salt, particularly an (*R*)(-) mandelate salt, a glutarate salt, an adipate salt, a squarate salt, a vanillate salt, an oxaloacetate salt, an ascorbate salt, particularly an (*L*)-ascorbate salt and a sulfate salt.
2. An acid addition salt selected from the group consisting of imatinib ascorbate, imatinib formate, imatinib malonate, imatinib oxaloacetate, imatinib squarate and imatinib vanillate.
3. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and an acid addition salt of 4-[(4-methyl-1-piperazinyl)methyl]-*N*-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]-benzamide selected from the group consisting of a tartrate salt, such as a (*D*)(-) tartrate salt or a (*L*)(+) tartrate salt, a hydrochloride salt, a citrate salt, a malate salt, particularly a *D*-malate salt, a fumarate salt, a succinate salt, a benzoate salt, a benzenesulfonate salt, a pamoate salt, a formate salt, a malonate salt, a 1,5-naphthalenedisulfonate salt, a salicylate salt, a cyclohexanesulfamate salt, a lactate salt, particularly a (*S*)-lactate salt, a mandelate salt, particularly an (*R*)(-) mandelate salt, a glutarate salt, an adipate salt, a squarate salt, a vanillate salt, an oxaloacetate salt, an ascorbate salt, particularly an (*L*)-ascorbate salt and a sulfate salt.
4. A pharmaceutical composition of claim 3 wherein the acid addition salt is selected from the group consisting of imatinib ascorbate, imatinib formate, imatinib malonate, imatinib oxaloacetate, imatinib squarate and imatinib vanillate.

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